The role of impaired neuronal communication in neurological disorders

Biyu J. He[a], Gordon L. Shulman[b], Abraham Z. Snyder[a] and Maurizio Corbetta[a,b,c]

Purpose of review

Basic and translational neuroscience findings indicate that normal brain function depends on activity synchronization within distributed brain networks. This conclusion suggests a view of how brain injury causes behavioral deficits that differs from traditional localizationist views.

Recent findings

Novel functional neuroimaging methods demonstrate coherent activity in large-scale networks not only during task performance but also, surprisingly, at rest (i.e. in the absence of stimuli, tasks, or overt responses). Furthermore, breakdown of activity coherence at rest, even in regions of the brain that are structurally intact, correlates with behavioral deficits and their recovery after injury. Breakdown of functional connectivity appears to occur not just after local injury but also in other conditions that affect large-scale neural communication.

Summary

A network perspective is fundamental to appreciating the pathophysiology of brain injury at the systems level and the underlying mechanisms of recovery, and for developing novel strategies of rehabilitation.

Keywords

brain injury, connectivity, functional magnetic resonance imaging, recovery of function, synchronization

Curr Opin Neurol 20:655–660.

[a]Department of Radiology, [b]Department of Neurology and [c]Department of Anatomy and Neurobiology, Washington University, St. Louis, Missouri, USA

Correspondence to M. Corbetta, Department of Neurology, Washington University School of Medicine, Box 8111, 660 S. Euclid Avenue, St. Louis, MO 63110, USA
E-mail: mau@npg.wustl.edu

Current Opinion in Neurology 2007, 20:655–660

Abbreviations

BOLD blood oxygen level dependent
fcMRI functional connectivity magnetic resonance imaging

1350-7540

Introduction

Clinicians commonly localize behavioral deficits to focal lesions in the brain. This principle of 'cortical localization of function' is a cornerstone of clinical practice based on two theoretical principles that were articulated in the 1800s. The first is that specific functions are represented in specific parts of the brain [1]. Second, injuries to the brain disrupt localized functions and give rise to corresponding behavioral deficits [2]. Although there remains debate concerning precisely what is localized within a given patch of brain, the general consensus is that complex functions such as language and memory emerge from the combination of much simpler elementary operations [1,3,4]. These principles have supported serial models of brain function in which stimuli (e.g. a word) are first analyzed in sensory areas, then associated with more abstract representations (e.g. meaning) in higher order associative areas, and finally reach the motor system where a response is generated. More sophisticated cognitive–anatomical models (see the report by Price [5] for language) assume a feed-forward stream of information processing, in which each region contributes a specific input/output operation. Although these localizationist ideas remain the theoretical backbone of clinical neurology, advances in neuroscience suggest a much more distributed, parallel, and recursive view of brain function that has deep implications for clinical practice.

It is well accepted that the brain is anatomically organized in widely distributed and highly parallel networks. For example, the visual system is arranged as a hierarchy of cortical areas, each connected bidirectionally with areas below and above it [6]. Moreover, many areas are horizontally connected with other areas at the same level. Critically, this anatomical arrangement emphasizes not just a bidirectional flow of information (bottom up from sensory to cognitive to motor areas, and top down from cognitive to sensory levels), but also local and long-range recursive processing through cortico-cortical or cortico-subcortical loops. In other words, perception of a stimulus or performance of a task requires the temporal coordination of multiple regions as the behavior unfolds.

Efficient transfer of information within the brain has long been assumed to depend on changes in the mean rate of spike discharge. Thus, presynaptic neurons transfer information by modulating their mean firing rate, which is integrated dendritically and which ultimately leads to a

change in the firing rate of postsynaptic neurons [7]. More recent results, however, emphasize the importance of rhythmic synchronization, which is a universal property of neural systems at the scale of neurons, small circuits, and widely distributed networks. Synchronization results in alternating periods of excitation and inhibition, which can respectively facilitate or inhibit the transfer of information [8]. Neurons probably communicate most effectively when their excitability fluctuations are synchronized. Conversely, a given anatomical connection is relatively ineffective when the connected neuronal groups are not synchronized (for review, see the paper by Fries [9]). There is a substantial and growing body of evidence that rhythmic synchronization plays a functional role in many cognitive functions (reviewed by Engel *et al.* [10] and Varela *et al.* [11]) as well as brain disorders [12••]. Furthermore, recent evidence indicates that brain networks exhibit synchronized spontaneous activity (i.e. they are 'functionally connected'), even in the absence of specific task performance (i.e. at 'rest'; see below).

These findings indicate that the function of any brain region cannot be understood in isolation but only in conjunction with the other regions ('network') with which it interacts at rest and during active behavior. The large-scale organization of the brain into distributed networks has important implications for our understanding of central nervous system disorders and brain–behavior relationships after brain injury. Some of these implications were foreseen many years ago by early neurologists such as Jackson, Andral, Prince, von Monakoff, and Head (reviewed by Finger [13]), who proposed that neurological deficits do not simply reflect the primary effect of a lesion but also the secondary effects of the lesion on other structures; 'Hence it follows that at the place where you discover a lesion there does not always reside the direct cause of the effects which are produced.' [14]. Furthermore, the damaged brain must be viewed as a whole new system, and not simply as the old system minus the lesioned parts; 'So far as the loss of function or negative manifestations are concerned . . . it is a new condition, the consequences of a fresh readjustment of the organism as a whole to the factors at work at the particular functional level disturbed by the local lesion.' [15].

Functional connectivity in healthy brains

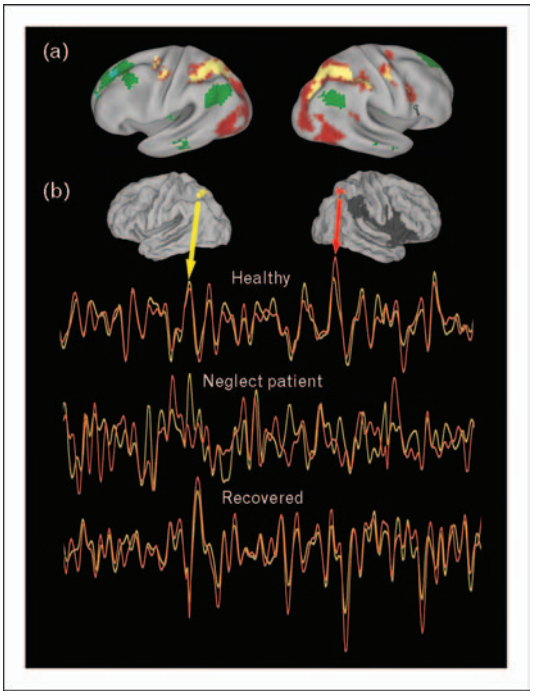
Functional neuroimaging techniques, especially positron emission tomography and functional magnetic resonance imaging, have greatly enhanced our understanding of the brain. Classically, neuroimaging experiments measure focal physiological responses induced by performance of externally imposed tasks. Such responses indirectly reflect changes in synaptic activity; these manifest as changes in regional cerebral blood flow with positron emission tomography, and as changes in the blood oxygenation level dependent (BOLD) signal with functional magnetic resonance imaging [16]. A large body of functional neuroimaging research indicates that anatomically consistent networks comprised of widely distributed regions activate and deactivate in concert across a wide range of tasks. For example, eye movements associated with viewing objects in the visual environment lead to consistently coupled activations in frontal and posterior parietal cortex [17]. Although co-occurrence of activations in different regions is suggestive of a network structure, more definitive evidence has come from analyses of temporal interactions between regions.

Over the past decade, several techniques have been developed to determine whether interactions between jointly activated regions produce enhanced temporal correlations in task-evoked responses. (For an earlier review, see Lee *et al.* [18•].) Unfortunately, these methods require an a-priori model of how regions are connected (for detailed reviews, see Penny *et al.* [19] and Stephan *et al.* [20]). Moreover, they are (invariably) contingent upon the specific task used, because changes in the system caused by external inputs are an integral part of the model. For examples of applications to patient populations, see [21–24].

As a result of these complicating factors, the strongest evidence for network structure based on temporal interactions between brain regions has come from the study of 'intrinsic' neural activity, that is, spontaneous activity observed as individuals lie quietly with their eyes either closed or simply fixated on a cross-hair. 'Functional connectivity MRI' (fcMRI) is a model-free strategy that measures the temporal correlation of the BOLD signal between brain regions, usually in the resting state [25–27,28•,29–32,33•].

fcMRI studies in neurologically normal, resting young adults have shown that spontaneous fluctuations in the BOLD signal are correlated within widely distributed networks that reproduce the topography typically seen in responses to controlled tasks. For example, regions commonly recruited by directed attention to environmental stimuli (Fig. 1) or performance of controlled cognitive tasks exhibit greater temporal correlations among themselves than with other regions, even in the resting state [30,31,34]. These intrinsic signal fluctuations are in part related to the underlying anatomical connectivity. For example, in monkeys fcMRI correlation maps involving lateral intraparietal area, the frontal eye fields, and functionally related temporal areas closely resemble the pattern of anatomical connectivity revealed by tract tracing [35••]. Similarly, in humans as well as monkeys, homologous regions of the cortex typically exhibit high functional connectivity [36], a finding that appears to

Figure 1 Functional connectivity in healthy subject and spatial neglect patient



(a) An example of functional connectivity obtained by measuring spontaneous BOLD signal fluctuations with functional magnetic resonance imaging (fMRI) in healthy individuals. Areas in yellow/red are temporally correlated and correspond to the 'dorsal attention network', which is important for the control of spatial attention. Areas in green/blue are negatively correlated with the dorsal attention network, and correspond to the 'default' network. (b) Randomly selected 10-min records of fMRI signals from the left (shown in yellow) and right (in red) posterior parietal cortex in an healthy elderly individual (top), an acute stroke patient with spatial neglect (middle), and in the same patient 9 months later when the behavioral deficits had recovered (bottom). Both regions are part of the dorsal attention network, and were outside of the lesion in this patient, which is shown in gray. In healthy individuals these two regions are coherent in their spontaneous fMRI fluctuations. Such temporal relationship is disrupted in patients with acute spatial neglect, but is regained during the course of recovery. Adapted with permission from He *et al.* [39••].

reflect inter-hemispheric connections through the corpus callosum. The correspondence between functional and anatomical connectivity is not one-to-one, however. For instance, although middle temporal area has strong direct connections to both area V_1 and the lateral intraparietal area, it has a stronger resting state temporal correlation with parietal than visual areas. These considerations suggest that fcMRI reflects anatomical connections that are somehow weighted by function.

Recent studies have investigated the neural signals that underlie the observed temporal correlations of the BOLD signal. Although BOLD fluctuations are slow (< 0.1 Hz), some evidence indicates that they might be related to power fluctuations of oscillatory neuronal activity at higher frequencies (1–200 Hz) [37]. Recent studies showed that different networks defined by fcMRI at rest are characterized by power fluctuations in electroencephalography signals [33•,38].

Critically, resting state fcMRI has been shown to be functionally significant in health, disease, and normal development. Thus, in healthy adults, functional connectivity in a language network was found to correlate with reading ability [28•]. Conversely, in stroke patients with spatial neglect, impaired functional connectivity in attention networks was observed to correspond to the severity of spatial perceptual deficits (see below) [39••]. Finally, the functional connectivity of networks involved in cognitive control was shown to be immature in children, corresponding to the poor performance of children relative to adults in tasks that are strongly dependent on cognitive control [40•].

Functional connectivity in injured brains

The overall organization of the brain into complex and distributed brain networks, identified by measuring temporal correlations in activity at rest and during behavior, suggests several predictions concerning the effects of a lesion on the brain's functional architecture. First, a focal injury will disrupt the synchronization between the site of damage and other connected regions, upstream and downstream, leading to changes in excitability throughout the network. Furthermore, changes in the state of one network may affect the dynamic state of other connected networks. Second, these altered patterns of activity in large-scale networks, whether measured at rest or during active behavior, should correlate with the observed neurological deficits. Behavioral deficits will reflect not only structural damage to a local part of a network but also functional imbalances throughout the network and in other connected networks. Finally, recovery of function involves the reorganization of entire brain networks. Rehabilitation may restore the networks to a normal state or enable a new state in which functions are performed through compensatory strategies.

To date, the most common functional pattern observed in patients with focal injury is a dynamic reorganization of the topography of task-related functional responses. For instance, Saur *et al.* [41••] tested a group of poststroke aphasic patients ($n = 14$) with an auditory comprehension task at three stages: acute (1.8 days poststroke), subacute (12 days), and chronic (321 days). They observed over the stages an improvement in language performance and increased activation of left hemisphere language regions (inferior frontal gyrus and middle temporal gyrus). In contrast, the homologous right hemisphere regions showed increased activity from acute to subacute stages, which correlated with improvement, followed by decreased activity at the chronic stage. A similar pattern of functional reorganization has been observed in primary

motor cortices (M_1) in patients with motor impairment after subcortical strokes (for review, see Ward [42•]). These findings have implications for treatment. Enhancement of excitability in ipsilesional M_1 by transcranial direct current stimulation significantly improved motor performance [43,44]. In contralesional M_1 increased excitability at the acute stage (< 1 month poststroke) was correlated with functional recovery [45], whereas at the chronic stage (> 12 months poststroke) a decrease in excitability significantly correlated with motor improvement [43].

The typical interpretation of these findings is that recruitment of contralesional regions may aid recovery at the acute and subacute stages, but may be maladaptive at the chronic stage, and that preservation or reactivation of ipsilesional activity affords the best chances of optimal recovery. A 'connectionist' interpretation suggests that these dynamic patterns of activation in the two hemispheres are linked and underlie changes in the functional communication within and between hemispheres caused by the lesion. For example, the lesion may abolish inhibitory influences over homologous areas in the opposite hemisphere mediated by callosal connections.

Changes in connectivity following a lesion occur rapidly and presumably depend on unmasking and changes in synaptic weights of pre-existing connections rather than the creation of new pathways. The rapidity of these changes is evident from a recent transcranial magnetic stimulation study conducted in healthy individuals [46••], which demonstrated that suppression of activity in left premotor cortex induces an immediate increase in activity in the contralateral premotor area that facilitates behavioral performance.

Inter-hemispheric or intra-hemispheric functional imbalances may also account for disrupted functional connectivity between two structurally intact regions that are directly or indirectly connected to an area of damage. A recent study of spatial neglect [47] showed that asymmetries in spatial attention correlated with imbalanced functional responses in structurally intact left and right dorsal parietal cortex. At the subacute stage, activity in right ipsilesional parietal cortex was relatively depressed during a spatial orienting task, whereas activity in contralesional left parietal cortex was relatively enhanced. This imbalance was behaviorally significant because the magnitude of activation in left parietal cortex correlated with the degree of spatial neglect. A recent follow-up study [39••] showed that this functional imbalance was also manifested in fcMRI measures (Fig. 1). Specifically, low inter-hemispheric coherence in parietal cortex correlated with worse neglect. Critically, in both studies the anatomical damage was located in the ventral frontal cortex, temporo-parietal junction and the underlying white matter, far removed from dorsal parietal regions where the functional signals were measured.

Conclusion

These novel findings provide a neurobiological basis for the intuition of early neurologists that what ultimately matters is the state of the network and not just what happens at the locus of injury. Knowing that a frontal lesion can cause functional changes in parietal cortex and that these changes are behaviorally significant not only provides a more complete understanding of brain–behavior relationships but also opens up the possibility of novel interventions. For instance, preliminary evidence indicates that rebalancing of activity across the hemisphere by suppressive transcranial magnetic stimulation improves performance [48,49].

This network approach also explains why acute stroke patients present multiple deficits that are not easily attributable to the locus of injury. For instance, a subcortical lesion may not only result in motor deficits but also impairments in language, attention, working memory, and task control. It is the rule that cognitive functions are almost never normal in patients with a focal brain injury. Whereas traditional explanations invoke non-neuronal factors such as edema, vascular dysregulation, and so on, a network perspective explains this multitude of problems by invoking disrupted neuronal communication within brain networks. fcMRI, potentially in association with simultaneous electroencephalogram recordings, is an especially promising approach to studying these network-level abnormalities because of its robustness (networks can be normally seen in a single subject after 5–15 min of scanning), reproducibility, and minimal task requirements that enable patients with a large range of deficits to be tested.

A final important point is that a network approach can also be applied to the study of nonfocal disorders such as Alzheimer's disease [50], depression [51•], and schizophrenia [52–54]. In Alzheimer's disease a breakdown of functional connectivity has been reported in the 'default' network [50], which is a set of brain regions that normally show task-related deactivations during controlled task performance [55] and that also are involved in memory retrieval [56]. In primary progressive aphasia, weakened functional connectivity during a language task between Broca's and Wernicke's regions correlated with the degree of language impairment [57•]. It is likely that a network approach using either fcMRI or more task-driven methods (see the review by Lee *et al.* [18•]) will be helpful in other disorders that affect large-scale cortical communication, as in the case of white matter lesions in multiple sclerosis [58] or disrupted interaction of basal ganglia and cortex in Huntington's disease [59].

Acknowledgements

Our research is supported by NINDS, NIMH, J.S. McDonnell foundation, and the European Union Marie Curie program.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issuze (p. 747).

1 Brodmann K. On the comparative localization of the cortex [originally in German; translated by von Bonin G]. In: Some papers on the cerebral cortex. Springfield, IL: Charles C Tomas; 1960. pp. 201–230.

2 Broca P. Localization of cerebral function. Siege of the language articulates [in French]. Bulletins de la Société d'Anthropologie (Paris) 1863; 4:200–203.

3 Ullman S. Visual routines. Cognition 1984; 18:97–159.

4 Posner MI, Petersen SE, Fox PT, Raichle ME. Localization of cognitive operations in the human brain. Science 1988; 240:1627–1631.

5 Price CJ. The anatomy of language: contributions from functional neuroimaging. J Anat 2000; 197 (Pt 3):335–359.

6 Felleman DJ, Van Essen DC. Distributed hierarchical processing in the primate cerebral cortex. Cereb Cortex 1991; 1:1–47.

7 Shadlen M, Britten KH, Newsome WT, Movshon JA. A computational analysis of the relationship between neuronal and behavioral responses to visual motion. J Neurosci 1996; 16:1486–1510.

8 Buzsaki G. Rhythms of the Brain. New York, NY: Oxford University Press; 2006.

9 Fries P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci 2005; 9:474–480.

10 Engel AK, Fries P, Singer W. Dynamic predictions: oscillations and synchrony in top-down processing. Nat Rev Neurosci 2001; 2:704–716.

11 Varela F, Lachaux JP, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci 2001; 2:229–239.

12 •• Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron 2006; 52:155–168.
This is a comprehensive review on oscillatory synchrony measured by electrophysiology, covering both methodology and applications to patient populations.

13 Finger S. Holism and the critics of localization. In: Origins of neuroscience. Oxford, UK: Oxford University Press; 1994. pp. 51–62.

14 Andral G. Medical clinic [in French]. Vol 4. Paris, France: Librairie Deville; 1833.

15 Head H. Some principles of neurology. Brain 1918; 41:344–354.

16 Raichle ME, Mintun MA. Brain work and brain imaging. Annu Rev Neurosci 2006; 29:449–476.

17 Corbetta M. Frontoparietal cortical networks for directing attention and the eye to visual locations: identical, independent, or overlapping neural systems. Proc Natl Acad Sci USA 1998; 95:831–838.

18 • Lee L, Friston K, Horwitz B. Large-scale neural models and dynamic causal modelling. Neuroimage 2006; 30:1243–1254.
A review of methods for the analysis of effective connectivity of task-evoked activity.

19 Penny WD, Stephan KE, Mechelli A, Friston KJ. Modelling functional integration: a comparison of structural equation and dynamic causal models. Neuroimage 2004; 23 (Suppl 1):S264–S274.

20 Stephan KE, Harrison LM, Kiebel SJ, *et al.* Dynamic causal models of neural system dynamics:current state and future extensions. J Biosci 2007; 32:129–144.

21 Hinrichs H, Heinze HJ, Schoenfeld MA. Causal visual interactions as revealed by an information theoretic measure and fMRI. Neuroimage 2006; 31:1051–1060.

22 Mechelli A, Allen P, Amaro E Jr, *et al.* Misattribution of speech and impaired connectivity in patients with auditory verbal hallucinations. Hum Brain Mapp 2007 [Epub ahead of print].

23 Seminowicz DA, Mayberg HS, McIntosh AR, *et al.* Limbic-frontal circuitry in major depression: a path modeling metanalysis. Neuroimage 2004; 22:409–418.

24 Schlosser R, Gesierich T, Kaufmann B, *et al.* Altered effective connectivity during working memory performance in schizophrenia: a study with fMRI and structural equation modeling. Neuroimage 2003; 19:751–763.

25 Biswal B, Yetkin F, Haughton V, Hyde J. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 1995; 34:537–541.

26 Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a nework analysis of the default mode hypothesis. Proc Natl Acad Sci USA 2003; 100:253–258.

27 Hampson M, Peterson BS, Skudlarski P, *et al.* Detection of functional connectivity using temporal correlations in MR images. Hum Brain Mapp 2002; 15:247–262.

28 • Hampson M, Tokoglu F, Sun Z, *et al.* Connectivity-behavior analysis reveals that functional connectivity between left BA39 and Broca's area varies with reading ability. Neuroimage 2006; 31:513–519.
This study showed the functional significance of spontaneous BOLD signal connectivity by correlating its strength between Broca's and Wernicke's areas with reading ability across a group of healthy individuals.

29 De Luca M, Smith S, Nicola De S, *et al.* Blood oxygenation level dependent contrast resting state networks are relevant to functional activity in the neocortical sensorimotor system. Experimental. Brain Res 2005; 167:587–594.

30 Fox MD, Snyder AZ, Vincent JL, *et al.* The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 2005; 102:9673–9678.

31 Fox MD, Corbetta M, Snyder AZ, *et al.* Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc Natl Acad Sci U S A 2006; 103:10046–10051.

32 Vincent JL, Snyder AZ, Fox MD, *et al.* Coherent spontaneous activity identifies a hippocampal-parietal memory network. J Neurophysiol 2006; 96:3517–3531.

33 • Mantini D, Perrucci MG, Del Gratta C, *et al.* Electrophysiological signatures of resting state networks in the human brain. Proc Natl Acad Sci U S A 2007; 104:13170–13175.
This simultaneous electroencephalography–fMRI study showed multiband electroencephalography power signatures for different resting state BOLD functional connectivity networks.

34 Dosenbach NU, Fair DA, Miezin FM, *et al.* Distinct brain networks for adaptive and stable task control in humans. Proc Natl Acad Sci U S A 2007; 104: 11073–11078.

35 •• Vincent JL, Patel GH, Fox MD, *et al.* Intrinsic functional architecture in the anaesthetized monkey brain. Nature 2007; 447:83–86.
This study showed, in anesthetized monkeys, that spontaneous BOLD signal connnectivity is independent of cognitive activity and is related to anatomical connections.

36 Salvador R, Suckling J, Coleman MR, *et al.* Neurophysiological architecture of functional magnetic resonance images of human brain. Cereb Cortex 2005; 15:1332–1342.

37 Leopold DA, Murayama Y, Logothetis NK. Very slow activity fluctuations in monkey visual cortex: implications for functional brain imaging. Cereb Cortex 2003; 13:422–433.

38 Laufs H, Krakow K, Sterzer P, *et al.* Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. Proc Natl Acad Sci U S A 2003; 100:11053–11058.

39 •• He BJ, Snyder AZ, Vincent JL, *et al.* Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron 2007; 53:905–918.
In patients with spatial neglect, disrupted functional connectivity in networks associated with control of spatial attention correlated with behavioral impairment.

40 • Fair DA, Dosenbach NU, Church JA, *et al.* Development of distinct control networks through segregation and integration. Proc Natl Acad Sci U S A 2007; 104:13507–13512.
This is an fcMRI study on the development of networks involved in task control, with implications for childhood attentional control disorders.

41 •• Saur D, Lange R, Baumgaertner A, *et al.* Dynamics of language reorganization after stroke. Brain 2006; 129:1371–1384.
This carefully conducted study showed the evolvement of task-evoked fMRI responses over the course of poststroke recovery in aphasia patients.

42 • Ward NS. The neural substrates of motor recovery after focal damage to the central nervous system. Arch Phys Med Rehabil 2006; 87:30–35.
An important review of the functional changes in the motor sytem after stroke.

43 Fregni F, Boggio PS, Mansur CG, *et al.* Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. NeuroReport 2005; 16: 1551–1555.

44 Hummel F, Celnik P, Giraux P, *et al.* Effects of noninvasive cortical stimulation on skilled motor function in chronic stroke. Brain 2005; 128:490–499.

45 Butefisch CM, Netz J, Wessling M, *et al.* Remote changes in cortical excitability after stroke. Brain 2003; 126:470–481.

46 •• O'Shea J, Johansen-Berg H, Trief D, *et al.* Functionally specific reorganization in human premotor cortex. Neuron 2007; 54:479–490.
Demonstration that acute inactivation by repetitive transcranial magnetic stimulation of left dorsal premotor cortex causes an increase in activity in homologous contralesional cortex that is compensatory for behavioral performance.

47 Corbetta M, Kincade MJ, Lewis C, *et al.* Neural basis and recovery of spatial attention deficits in spatial neglect. Nat Neurosci 2005; 8:1603–1610.

48 Brighina F, Bisiach E, Oliveri M, *et al.* 1 Hz repetitive transcranial magnetic stimulation of the unaffected hemisphere ameliorates contralesional visuospatial neglect in humans. Neurosci Lett 2003; 336:131–133.

49 Naeser MA, Martin PI, Nicholas M, *et al.* Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. Brain Lang 2005; 93:95–105.

50 Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci USA 2004; 101:4637–4642.

51 • Greicius MD, Flores BH, Menon V, *et al.* Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol Psychiatry 2007; 62:429–437.
This study shows abnormal functional connectivity in depression.

52 Buckholtz JW, Meyer-Lindenberg A, Honea RA, *et al.* Allelic variation in RGS4 impacts functional and structural connectivity in the human brain. J Neurosci 2007; 27:1584–1593.

53 Kubicki M, McCarley R, Westin CF, *et al.* A review of diffusion tensor imaging studies in schizophrenia. J Psychiatr Res 2007; 41:15–30.

54 Zhou Y, Liang M, Jiang T, *et al.* Functional disconnectivity of the dorsolateral prefrontal cortex in first-episode schizophrenia using resting-state fMRI. Neurosci Lett 2007; 417:297–302.

55 Shulman GL, Fiez JA, Corbetta M, *et al.* Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. J Cogn Neurosci 1997; 9:648–663.

56 Buckner RL, Snyder AZ, Shannon BJ, *et al.* Molecular, structural and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J Neurosci 2005; 25:7709–7717.

57 • Sonty SP, Mesulam MM, Weintraub S, *et al.* Altered effective connectivity within the language network in primary progressive aphasia. J Neurosci 2007; 27:1334–1345.
Using dynamic causal modeling, this study showed reduced effective connectivity between Wernicke's and Broca's areas in patients with primary progressive aphasia.

58 Cader S, Cifelli A, Abu-Omar Y, *et al.* Reduced brain functional reserve and altered functional connectivity in patients with multiple sclerosis. Brain 2006; 129:527–537.

59 Thiruvady DR, Georgiou-Karistianis N, Egan GF, *et al.* Functional connectivity of the prefrontal cortex in Huntington's disease. J Neurol Neurosurg Psychiatry 2007; 78:127–133.